

Amyloid Deposition Modifies The Association Of CSF Vascular Markers With Cognitive Function

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Background



Blood-brain barrier (BBB) dysfunction is associated with cognitive decline and may play a contributory role in AD pathogenesis¹.

Markers of brain vascular damage and BBB disruption such as platelet-derived growth factor receptor-β (PDGFRβ) and Lipocalin-2 (LCN2) could be potential biomarkers for cognitive decline and AD progression^{2,3}.

Aim

Evaluate the association of CSF PDGFRβ and LCN2 with changes in vascular damage and cognitive function along the preclinical phase of AD.

Methods



Participants

CSF samples from 234 subjective cognitive decline (SCD) individuals from the Barcelonaβeta Brain Research Centre's Alzheimer's At-Risk Cohort [β-AARC] (mean age: 66.5 years, 44% females and 24% amyloid positive. Individuals where followed-up every year for a total of three visits.

Cognitive fucion

Preclinical Alzheimer Cognitive Composite (PACC) score, to detect the first signs of cognitive impairment, was assessed from the three visits.

Vascular damage

White Matter Hyperintensities (WMH) were analyzed at baseline as a sign of vascular damage. They were determined by MRI-TFE and FLAIR sequences across the first visit.

CSF PDGFRβ and LCN2 measurements

Levles of CSF PDGFRβ and LCN2 were measured using Human Total PDGFR beta DuoSet IC ELISA, Biotechne (R&D) and Human Lipocalin-2/NGAL Quantikine, Biotechne (R&D), respectively.

Statistical analysis

Linear models and linear mixed effect models were used to assess the association of PDGFRβ and LCN2 with PACC and WMH at baseline levels, and PACC at longitudinal levels, respectively.

Results

CSF PDGFRβ is increased in preclinical AD

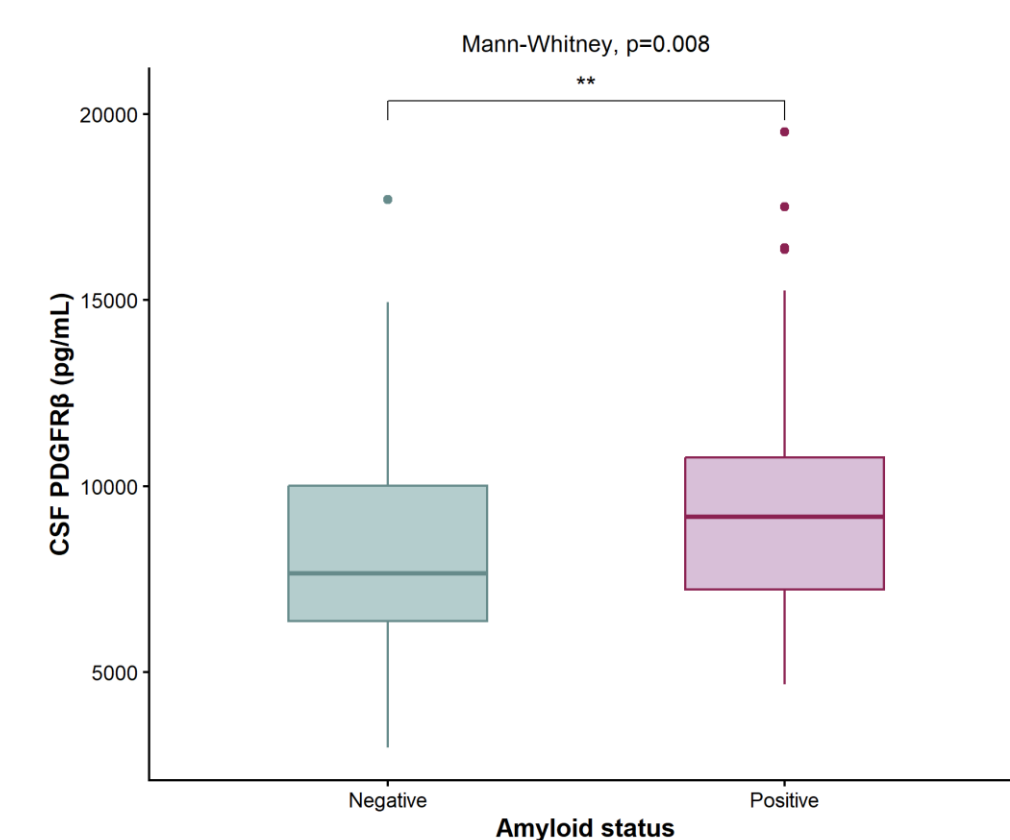


Figure 1. CSF PDGFRβ levels comparison according to the Amyloid status. Box plots showing the distribution of each group. Group differences were assessed with a two-sided Mann–Whitney U test. *p-value below significance threshold of 0.05.

CSF PDGFRβ is negatively associated with chronic brain vascular damage in Amyloid negative individuals

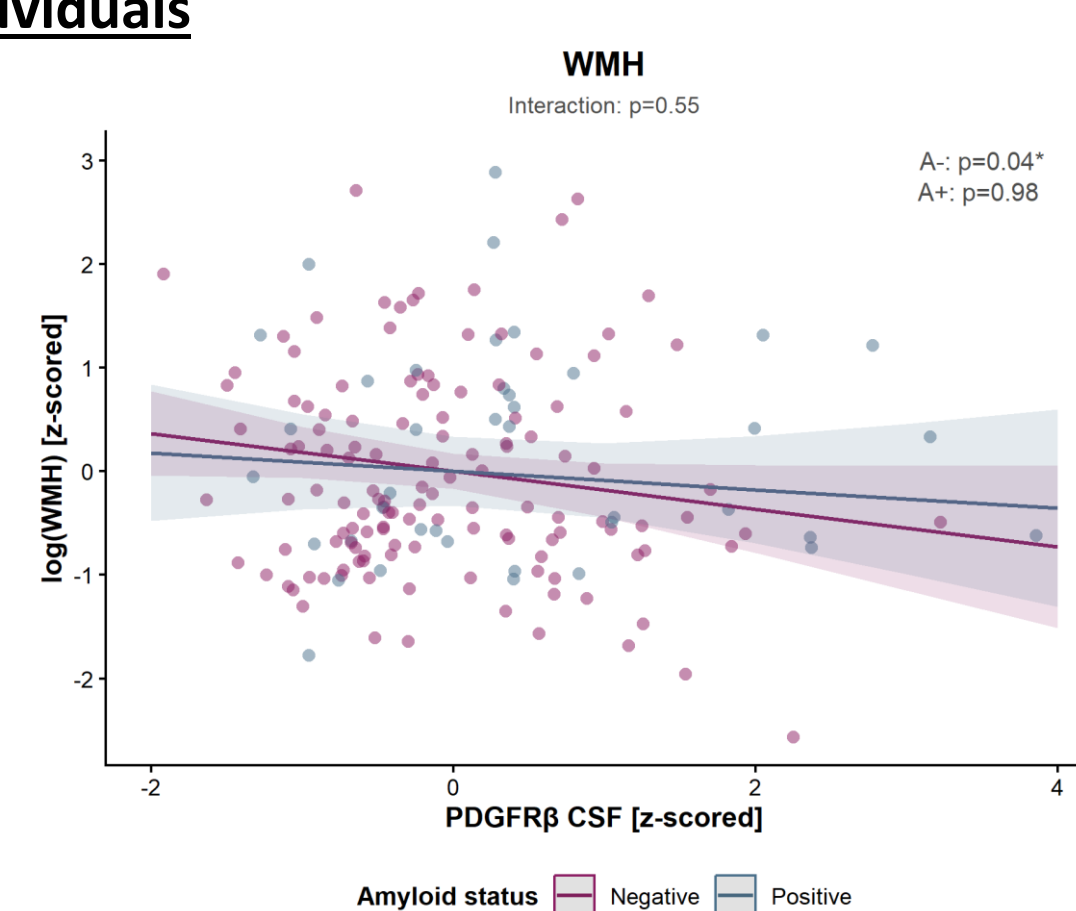


Figure 2. Linear model predicting the association of CSF PDGFRβ with WMH. The model was corrected by age and stratified by Amyloid status. A-: Amyloid negative; A+: Amyloid positive. The interaction term refers to the difference between A+ and A- individuals. *p-value below significance threshold of 0.05.

CSF PDGFRβ is not associated with cognitive function in individuals with preclinical AD; however, Amyloid negative individuals present higher tendencies

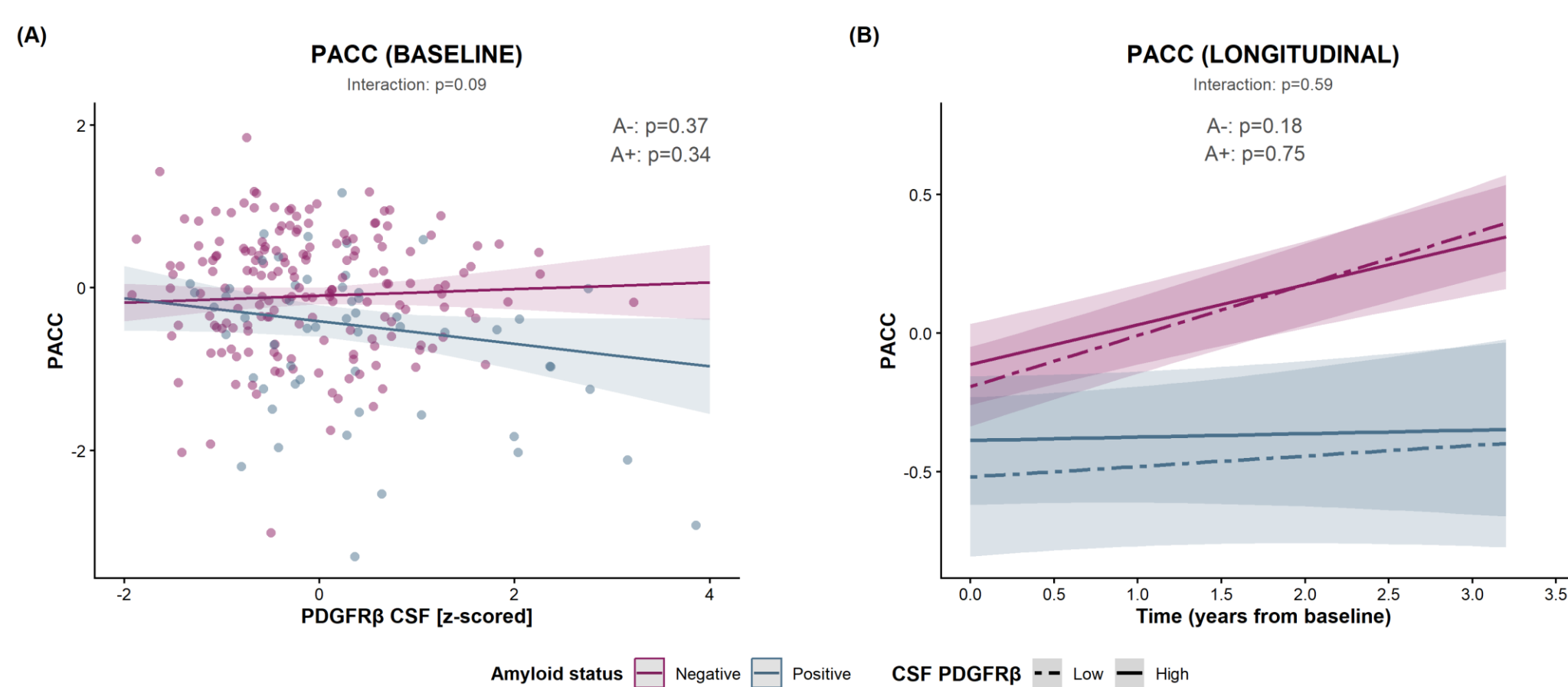


Figure 3. Linear model and linear mix effect model predicting the association of CSF LCN2 with WMH at a baseline (A) and longitudinal level (B), respectively. The models were corrected by age, years of education and body mass index (BMI), and stratified by Amyloid status. A-: Amyloid negative; A+: Amyloid positive. The interaction term refers to the difference between A+ and A- individuals. *p-value below significance threshold of 0.05.

CSF LCN2 does not vary depending on the Amyloid status

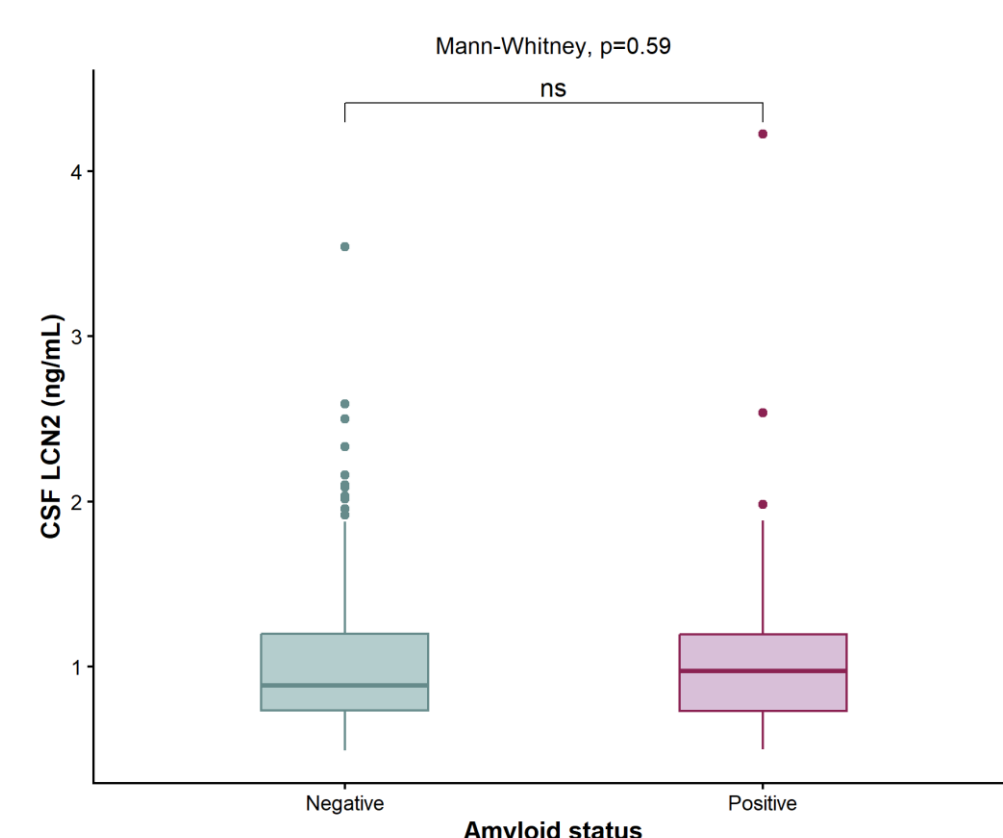


Figure 4. CSF LCN2 levels comparison according to Amyloid status. Box plots showing the distribution of each group. Group differences were assessed using a two-sided Mann–Whitney U test. *p-value below significance threshold of 0.05.

CSF LCN2 is increased in males

CSF LCN2 levels were significantly different in females and males.

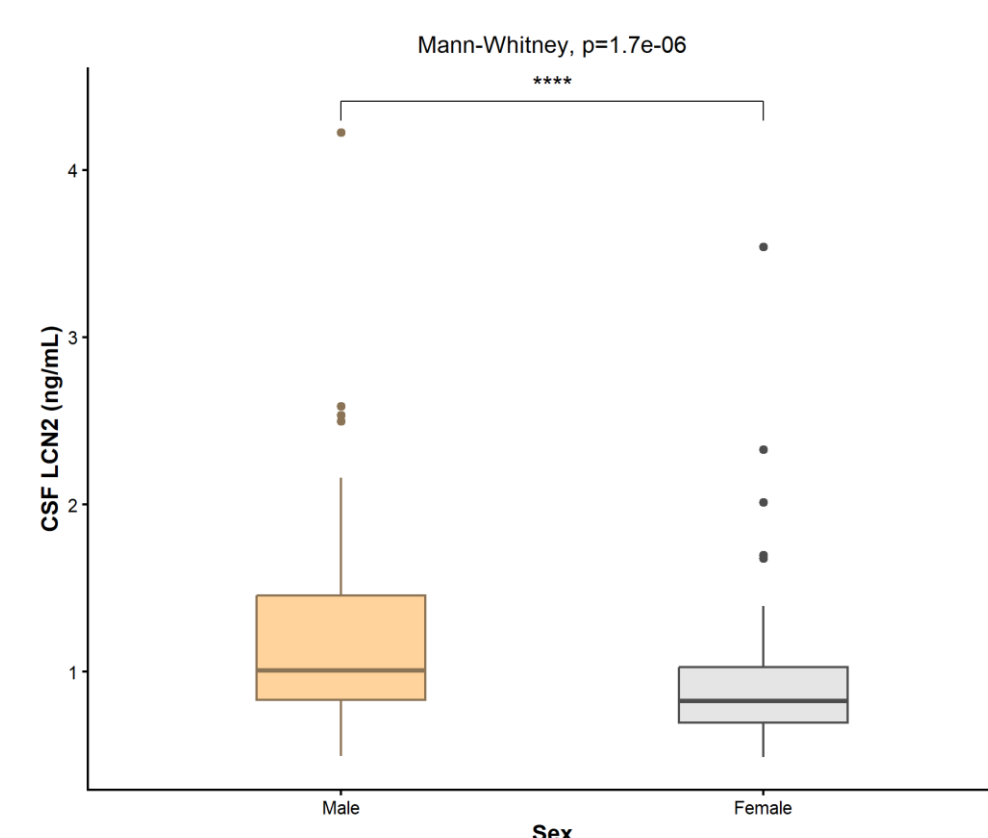
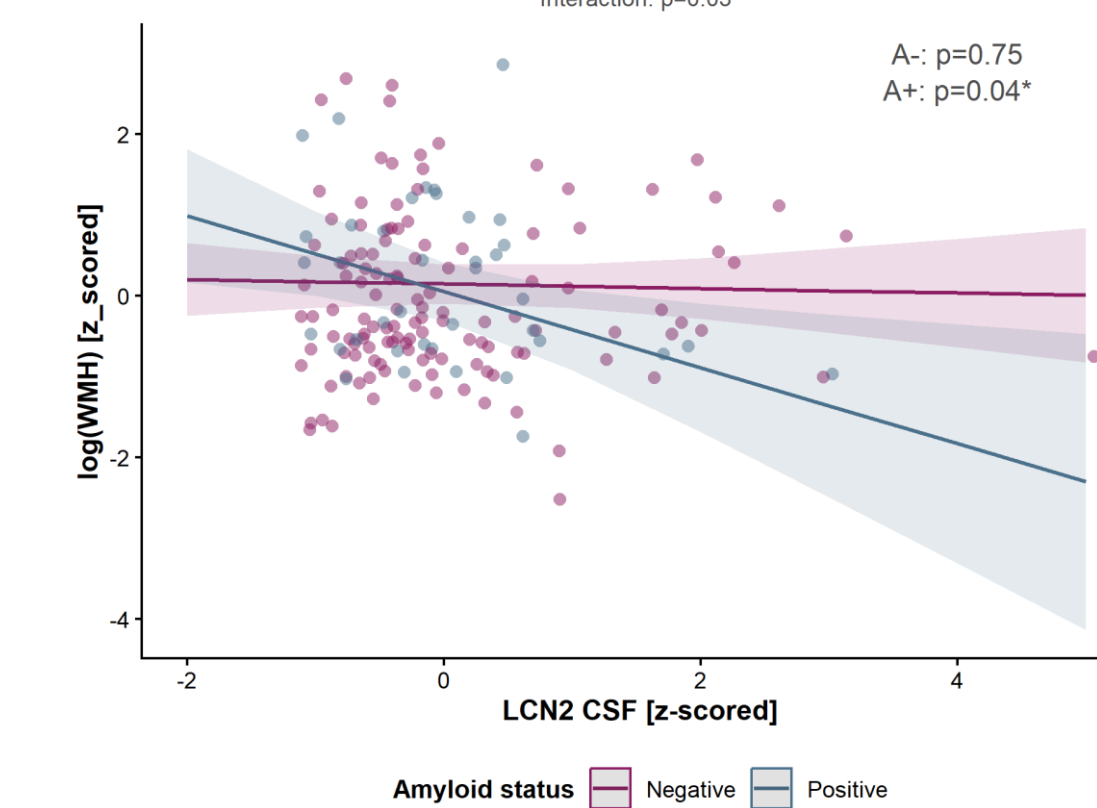


Figure 5. CSF LCN2 levels comparison according to sex. Box plots showing the distribution of each group. Group differences were assessed using a two-sided Mann–Whitney U test. *p-value below significance threshold of 0.05.

CSF LCN2 is negatively associated with chronic brain vascular damage in Amyloid positive individuals



CSF LCN2 levels are differently associated with WMH depending on the Amyloid status. Higher CSF LCN2 levels are observed when reduced WMH.

Figure 6. Linear models predicting the association of CSF LCN2 with WMH. model was corrected by age and sex and stratified by Amyloid status. A-: Amyloid negative; A+: Amyloid positive; F: female; M: male. The interaction term refers to the difference between A+ and A- individuals in (A), and between F and M in (B). *p-value below significance threshold of 0.05.

CSF LCN2 is differently associated with cognitive function over time depending on the Amyloid status

CSF LCN2 is not associated with PACC at baseline levels. However, Amyloid negative and positive individuals present contrary trajectories (Figure 7A). At a longitudinal level, participants with lower CSF LCN2 levels present similar trajectories independently of the Amyloid status, whereas individuals with higher CSF LCN2 concentrations have significant different trajectories: PACC levels tend to increase in Amyloid negative individuals, whereas in Amyloid positive slightly decrease (Figure 7B).

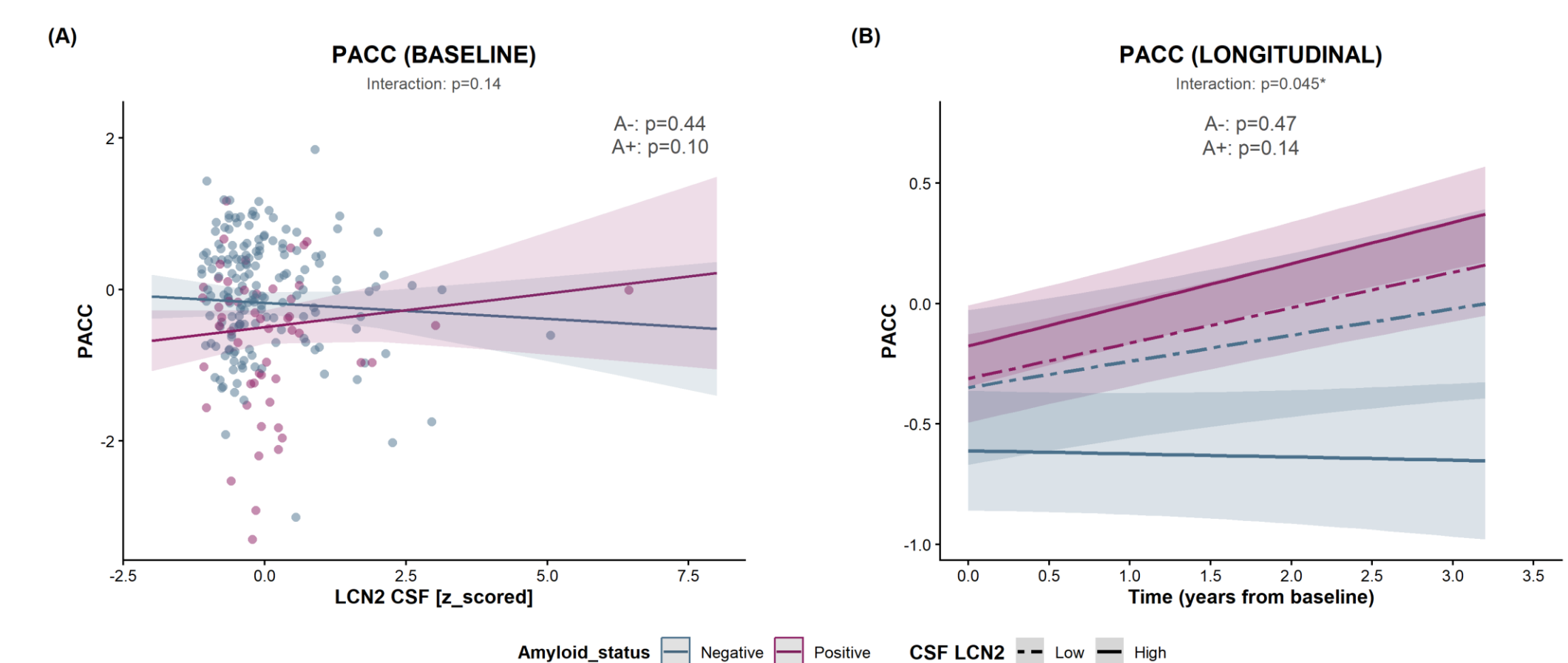


Figure 7. Linear model and linear mix effect model predicting the association of CSF LCN2 with PACC at a baseline (A) and longitudinal level (B), respectively. The models were corrected by age, years of education and BMI, and stratified by Amyloid status. A-: Amyloid negative; A+: Amyloid positive. The interaction term refers to the difference between A+ and A- individuals. *p-value below significance threshold of 0.05.

Conclusions

- Amyloid pathology in preclinical stage modify the association of markers related to pericyte injury or BBB disruption with vascular and cognitive function over time.
- CSF PDGFRβ can not predict cognitive decline over time in preclinical AD.
- Lower levels of CSF LCN2, but not PDGFRβ reflect higher levels of WMH in Amyloid positive individuals, suggesting it as a potential marker of vascular injury in preclinical AD.
- CSF LCN2 levels differ between sex, but it does not influence the association of this marker with cognitive or imaging outcomes.
- Upcoming analysis will reveal the association of these markers in plasma with cardiovascular risk profiles and imaging markers of vascular pathology.

Acknowledgements

The authors would like to express their most sincere gratitude to the β-AARC project participants and relatives without whom this research would not have been possible.